REMARKS

Claim 22 has been amended to delete reference to the figures. Claim 27 has been deleted. Claims 22-26 are presented for examination. Applicants respond below to the specific rejections raised by the Examiner in the final Office Action mailed June 23, 2004. For the reasons set forth below, Applicants respectfully traverse.

Rejection under 35 U.S.C. §101 – Utility

The PTO has rejected Claims 22-27 under 35 U.S.C. § 101 as lacking patentable utility. The PTO concedes that the cited utilities are credible. However, the PTO alleges that the invention lacks both substantial and specific utility. Applicants respectfully disagree.

Utility – Legal Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic tool without also identifying the condition that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. § 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, *any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient,* at least with regard to defining a 'substantial' utility." (M.P.E.P. § 2107.01, emphasis added.)

Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. § 2107 II(B)(1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular

practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Utility – Evidentiary Standard

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). See, also *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977).

Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, **the PTO must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility.** Only after the PTO has made a proper *prima facie* showing of lack of utility does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

Substantial Utility

The PTO argues that the invention lacks substantial utility because the evidence in the specification that the level of overexpression in cancer cells of the nucleic acid which encodes the PRO1800 protein was minimal, and there is no evidence that overexpression is significant or a real effect and not simply produced by chance. In addition, the PTO argues that the invention lacks utility because the overexpression of the nucleic acid is not relevant to the utility of the protein and antibody and there is no evidence that the protein is overexpressed. The PTO cites two references, Pennica *et al.* (Proc. Natl. Acad. Sci. (1998) 95:14717-14722) (hereinafter Pennica), and Konopka (Proc. Natl. Acad. Sci. (1986) 83:4049-4052) (hereinafter Konopka) to support its position that there is no necessary correlation between nucleic acid expression and protein expression. The PTO states that Pennica show that the *Wisp-2* DNA was amplified but

the RNA expression was reduced in tumors, while Konopka shows that protein expression is not related to amplification of the *abl* gene but to variation in the level of the *bcr-abl* mRNA produced from a single Ph^1 template. From these two examples, neither of which are related to the claimed invention, the PTO concludes that because there is no necessary connection between the level of protein in a cell and the amount of mRNA, and no necessary connection between the amount of DNA in a cell and the amount of mRNA, any evidence of overexpression of one component does not provide utility for the protein.

The PTO also argues that the art supports the conclusion that many genes are irrelevant in gene microarrays. Relying on Li *et al.* (J. Theoretical Biology (2002) 219: 513-551) (hereinafter Li), Ding *et al.* (Bioinformatics (2003) 19(10):1259-66) (hereinafter Ding), and Sawiris *et al.* (Cancer Research (2002) 62:2923-2928) (hereinafter Sawiris), the PTO concludes that "the overwhelming state of the art supports the position that many genes are irrelevant, that genes whose expression does not change are noise, and that these irrelevant genes are so insignificant that ideally they are not placed on the arrays or used at all." Therefore, the PTO concludes that such genes lack substantial utility as useful on gene expression arrays.

Applicants have established that the gene encoding the PRO1800 polypeptide is overexpressed in certain cancers

Applicants first address the PTO's argument that the level of overexpression of nucleic acid encoding PRO1800 was minimal and insignificant. Applicants submit that the gene amplification data provided in the present application are sufficient to establish a specific and substantial utility for the PRO1800 polypeptide and antibody.

Gene amplification is an essential mechanism for oncogene activation. It is well known that gene amplification occurs in most solid tumors, and generally is associated with poor prognosis. As described in Example 16 of the present application, the inventors isolated genomic DNA from a variety of primary cancers and cancer cell lines that are listed in Table 6 (Table 7 as amended, page 114 of the specification). As a negative control, DNA was isolated from the blood of normal healthy individuals (page 112, lines 7-9). Gene amplification was monitored using real-time quantitative TaqMan™ PCR. The gene amplification results are set forth in Table 7 (Table 8 as amended, page 117 of the specification). As explained in the specification on page 112, lines 17-19, the results of TaqMan™ PCR are reported in ΔCt units. It is well-known in the art that "Ct" stands for "threshold cycle." One Ct unit corresponds to one PCR cycle or

approximately a 2-fold amplification, relative to control, two units correspond to 4-fold, 3 units to 8-fold, etc. amplification.

It is well-known in the art how ΔCt values are calculated. The TaqMan™ real-time PCR method, which is the used in the methods of the present application, has gained wide recognition for its versatility, sensitivity and accuracy, and is in extensive use for the study of gene amplification. The TaqMan™ 7700 Sequence Detector Software calculates the Ct values for each given experiment. Those of skill in the art know that to obtain ΔCt, the difference between the Ct values of the test sample and the normal sample is calculated. Furthermore, the specification itself teaches that "The diluted samples were used provided that the CT value of the normal human DNA subtracted from test DNA was +/- 1 Ct" (specification at page 116, lines 30-31). Thus, the specification teaches that ΔCt is obtained when the Ct value of the normal sample is subtracted from the Ct value of the test sample.

In support of Applicants' assertion of utility, Applicants submitted a copy of the declaration of Dr. Audrey Goddard with exhibits A-G (the Goddard Declaration), with the Amendment and Response to Office Action, mailed August 4, 2003. As has been previously pointed out, Dr. Goddard's *curriculum vitae*, Exhibit A of the Goddard Declaration, shows, she is an expert in the art of identifying and quantifying the amplification of oncogenes in cancers.

In her declaration, Dr. Goddard states that:

> the quantitative TaqMan PCR technique is technically sensitive enough to detect at least a 2-fold increase in gene copy number relative to control. It is further my considered scientific opinion that an at least 2-fold increase in gene copy number in a tumor tissue sample relative to a normal (i.e., non-tumor) sample is significant and useful in that the detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number as quantitated by the TaqMan PCR technique as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology. Accordingly, a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is useful as a marker for the diagnosis of cancer, for monitoring cancer development and/or for measuring the efficacy of cancer therapy.

The Goddard Declaration, paragraph 7. Therefore, according to Dr. Goddard, a 2-fold increase, i.e., a ΔCt value of 1, not only is <u>not</u> of questionable significance, but is "significant and useful" in, *inter alia*, detecting cancerous tumors or the diagnosis of cancer. Thus, the Goddard Declaration support Applicants' position that the ΔCt value of 1 or more is significant and is

outside of the experimental error of this procedure. As is indicated in Table 7 (Table 8 as amended), the ΔCt value for PRO1800 is greater than 1 for several tumor cell types, indicating a more than 2-fold amplification. The PTO has offered no evidence which casts doubt on the conclusions of the Goddard declaration that the results of Table 7 (Table 8 as amended) are significant, useful, and thus not simply artifacts. Applicants remind the Examiner that "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered." PTO Utility Examination Guidelines (2001). Applicants therefore submit that they have established that the PRO1800 gene is amplified in certain tumor cells.

This argument along with the Goddard Declaration was presented to Examiner Fredman in the closely related and co-owned patent application Serial No. 10/033,167 to overcome a nearly identical 35 U.S.C. § 101 utility rejection. That closely related application is directed in part to the nucleic acid sequence encoding the PRO539 protein and contains the same data presented and relied on in the instant application. In that case, the PTO concluded that the Goddard declaration was "sufficient to overcome the rejection of the claims based upon utility and enablement as discussed above." (Office Action dated 9/9/2003, page 5, paragraph 8).

Applicants have established that the accepted understanding in the art is that there is a direct correlation between an increase in gene expression and the level of the encoded protein

Applicant next addresses the PTO's argument that there is no necessary correlation between level of protein in a cell and the amount of nucleic acid. Citing two references, the PTO correctly states that increased gene copy number does not *necessarily* result in increased protein expression. The PTO states that a *prima facie* case of lack of utility has been established based at least in part on these two references. The M.P.E.P. § 2107 Guidelines for Utility Examination clearly state that "[w]here the asserted utility is not specific or substantial, **a *prima facie* showing must establish that it is more likely than not that a person of ordinary skill in the art** would not consider that any utility asserted by the applicant would be specific and substantial." (emphasis added). The M.P.E.P. also states that the *prima facie* showing must contain the "[s]upport for the factual findings relied upon" in reaching the conclusion that the utility is not substantial and specific. Thus, the initial burden is on the PTO to establish that it is more likely than not that one of skill in the art would not consider the asserted utility substantial, and that

conclusion must be supported. Applicants submit that the two references cited, even if they supported the PTO's position, are only two examples of an alleged lack of correlation between gene amplification and mRNA or protein expression. The two references are not sufficient to establish that it is more likely than not that a person of ordinary skill in the art would not consider the asserted utility to be substantial.

The Pennica reference does not support the PTO's argument that because gene amplification is not necessarily correlated to mRNA level, there is no correlation between nucleic acid levels and protein expression. The PTO focuses on the statement from the abstract of Pennica that the *WISP-2* gene DNA was amplified in colon tumors, but RNA expression was reduced in 79% of the tumors. (Pennica at 14717). This inverse correlation is in contrast to the *WISP-1* gene, which was amplified and had higher RNA levels. The authors of Pennica offer an explanation for what they obviously viewed as an anomalous result: "Because the center of the 20q13 amplicon [of which *WISP-2* is a part] has not yet been identified, it is possible that the *apparent amplification* observed for *WISP-2* may be caused by another gene in this amplicon." (*Id.* at 14722.) Thus, the example of a lack of positive correlation between gene amplification and RNA levels relied on by the PTO may not actually be real. The fact that the authors attempt to explain this anomaly only supports Applicants' argument that the accepted understanding in the art is that there is a direct correlation between an increase in gene expression and the level of the encoded protein

Similarly, a reading of the entire Konopka reference reveals that it does not support the PTO's argument that there is no correlation between nucleic acid levels and protein expression. Konopka reports on the expression of the translocated *c-abl* oncogene, known as the Philadelphia chromosome, or Ph^1. (Konopka at 4049.) In the cancer cells studied, the Ph^1 translocation creates a chimeric *abl* gene, *bcr-abl*, that encodes a structurally altered form of the *abl* oncogene product, known as $P210^{c\text{-}abl}$. As Konopka reports, "the 8-kb mRNA that encodes $P210^{c\text{-}abl}$ was detected at 10-fold higher level in [cell type A] than in [cell type B], **which correlated with the relative level of $P210^{c\text{-}abl}$ detected in each cell line.**" (*Id.* at 4050). Thus, as Applicants have asserted is most usually the case, the level of protein was correlated with the level of mRNA. Not surprisingly, as the abstract reports, the level of protein expression of $P210^{c\text{-}abl}$ is not related to the amplification of the unaltered *abl* gene, but instead correlates to the level of mRNA for the chimeric *bcr-abl* gene, which is the product of the translocation Ph^1. Thus the PTO's reliance on

the abstract to support their argument that there is no correlation between nucleic acid levels and protein expression is misplaced.

The standard for utility is not absolute certainty, but rather whether one of skill in the art would be more likely than not to believe the asserted utility. Even if the cited references supported the PTO's argument, which they do not, the fact that in specific cases there seemed to be no correlation between gene amplification and the level of mRNA/protein expression does not establish that one of skill in the art would find it is more likely than not, that in general, such correlation does not exist. In fact, the working hypothesis among those skilled in the art is that if a gene is amplified in cancer, the encoded protein is likely to be expressed at an elevated level.

Applicants have previously presented a copy of a Declaration by J. Christopher Grimaldi, an expert in the field of cancer biology. This declaration was submitted in connection with co-pending application Serial No. 10/006,867. As stated in paragraph 5 of the declaration, "Those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed...the gene product or polypeptide will also be overexpressed." The references cited in, and submitted with, the declaration support this statement.

Applicants also submit herewith a copy of the declaration of Paul Polakis, Ph.D., an expert in the field of cancer biology, originally submitted in a related and co-owned patent application Serial No. 10/032,996. As stated in paragraph 6 of his declaration:

> Based on my own experience accumulated in more than 20 years of research, including the data discussed in paragraphs 4 and 5 above and my knowledge of the relevant scientific literature, it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell. In fact, *it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein.* (Emphasis added).

Dr. Polakis acknowledges that there are published cases where such a correlation does not exist, but states that it is his opinion that "such reports are exceptions to the commonly understood general rule that increased mRNA levels are predictive of corresponding increased levels of the encoded protein." (Polakis Declaration, paragraph 6).

Together, the declarations of Mr. Grimaldi and Dr. Polakis establish that the accepted understanding in the art is that there is a direct correlation between an increase in gene expression and the level of the encoded protein. In light of the lack of support for any argument

by the PTO to the contrary, Applicants submit that they have established that it is more likely than not that one of skill in the art would believe that because the gene encoding the PRO1800 polypeptide is overexpressed in certain cancers, the PRO1800 polypeptide will also be overexpressed in those cancers.

Claimed antibodies would have diagnostic utility even if the protein were not over-expressed

Even assuming *arguendo* that, there is no correlation between gene expression and increased protein expression for PRO1800, which Applicants submit is not true, a polypeptide encoded by a gene that is over-expressed in cancer would **still** have a substantial utility. In support, Applicants have submitted the Declaration of Avi Ashkenazi, Ph.D., an expert in the field of cancer biology. Dr. Ashkenazi's Declaration explains that:

> even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment. Thus, *if over-expression of the gene product does not parallel gene amplification in certain tumor types but does so in others, then parallel monitoring of gene amplification and gene product over-expression enables more accurate tumor classification and hence better determination of suitable therapy.* In addition, absence of over-expression is crucial information for the practicing clinician. If a gene is amplified but the corresponding gene product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product. (Ashkenazi Declaration, paragraph 6, emphasis added).

Applicants submit that simultaneous testing of gene expression (or gene amplification) and gene product over-expression enables more accurate tumor classification, even if the gene-product, the protein, is not over-expressed. This leads to better determination of a suitable therapy. Further, as explained in Dr. Ashkenazi's Declaration, absence of over-expression of the protein itself is crucial information for the practicing clinician. If a gene is amplified in a tumor, but the corresponding gene product is not over-expressed, the clinician need not treat a patient with agents that target that gene product. This not only saves money, but further prevents unnecessary exposure of the patient to the side effects of gene product targeted agents.

This is further supported by the teachings in the article by Hanna and Mornin, submitted herewith. The article teaches that the HER-2/neu gene has been shown to be amplified and/or over-expressed in 10%-30% of invasive breast cancers and in 40-60% of intraductal breast carcinoma. Further, the article teaches that diagnosis of breast cancer includes testing both the

amplification of the HER-2/neu gene (by FISH) as well as the over-expression of the HER-2/neu gene product (by IHC). Even when the protein is not over-expressed, the assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it.

The art indicates that, if a gene is amplified in cancer, it is **more likely than not** that the encoded protein will also be expressed at an elevated level. Even if not over-expressed, a polypeptide encoded by a gene that is over-expressed in cancer would still have utility. Thus, Applicants have demonstrated a substantial asserted utility for the PRO1800 polypeptide and antibodies. Based on the evidence and arguments presented herein, one skilled in the art, at the time the application was filed, would know how to use the claimed antibodies.

Genes overexpressed in cancers are useful diagnostic tools

Applicants next address the PTO's argument that the art supports the conclusion that many genes are irrelevant in gene microarrays. Relying on Li, Ding, and Sawiris, the PTO concludes that "the overwhelming state of the art supports the position that many genes are irrelevant, that genes whose expression does not change are noise, and that these irrelevant genes are so insignificant that ideally they are not placed on the arrays or used at all." Therefore, the PTO concludes that such genes lack substantial utility as useful on gene expression arrays.

Applicants do not dispute that many genes are irrelevant when it comes to use in gene microarrays. However, the cited references do not support the PTO's conclusion that a gene which is significantly overexpressed in certain cancer cells, such as the gene which encodes PRO1800, is not useful in a gene microarray. The cited statements from Li, that there are important and irrelevant genes and that it is useful to remove the irrelevant genes from microarrays, are statements of the obvious, and offer no support for an argument that the gene encoding PRO1800 is one of the irrelevant genes. To the contrary, Li goes on to analyze an example of a microarray used to distinguish cancerous tissue from normal tissue. (Li at 543.) The authors state that in making such a distinction, they are most interested in genes that are expressed higher in cancerous tissues than in normal tissues. (*Id.*) Thus, Li teaches that the gene encoding PRO1800 is an example of a gene that would be of interest.

Likewise, the PTO cites Ding for the proposition that genes without changes in expression profiling should be discarded as irrelevant. Regardless of the merits of the novel method disclosed in Ding, PRO1800 does show a change in expression profile between lung and colon tumors and normal tissue. Thus, nothing in Ding supports the PTO's conclusion that a

gene which is significantly overexpressed in certain cancer cells, such as the gene encoding PRO1800, is not useful in a gene microarray.

Finally, the PTO cites Sawiris for the obvious statement that "[o]ne of the advantages of specialized arrays is that they do not include irrelevant genes that may contribute to noise during data analysis." What the PTO fails to note is that the genes that were chosen for inclusion in the specialized chip were those that were either overexpressed or underexpressed in ovarian cancer. (Sawiris at 2923, second column.) Thus, contrary to the PTO's assertions, the gene encoding PRO1800 is useful for microarrays since it is overexpressed in certain colon and lung tumors.

The three references cited do not support the PTO's rejection of the asserted utility of using the gene encoding PRO1800 as a diagnostic agent for cancer. While the PTO's statement that the prior art supports the conclusion that there are many irrelevant genes is not disputed, none of the references support the conclusion that the gene encoding PRO1800 is one of those irrelevant genes when it comes to a diagnostic tool for cancer, particularly colon and lung cancer. To the contrary, the references indicate that the relevant genes are those that are overexpressed or underexpressed in the cancer of interest, genes like the one which encodes PRO1800. Thus Applicants submit that the PTO has failed to offer any support for its conclusion that the gene encoding PRO1800 is not useful as a cancer diagnostic tool. In the absence of such support, the PTO has failed to establish a *prima facie* case of lack of substantial utility.

As discussed above, using a widely accepted technique, Applicants have generated data showing that the gene encoding the PRO1800 polypeptide is amplified in cancerous tissue. Applicants have submitted the declarations of experts in the field which indicate that the overexpression of the gene in cancer cells makes it a useful diagnostic tool. (See Goddard Declaration, paragraph 7; Ashkenazi Declaration, paragraph 5). The PTO offers no support for its assertion that the gene is not useful as a diagnostic tool, instead merely citing references which state the obvious – not all genes are relevant in microarrays. Likewise, the Applicants have established that the general, accepted understanding in the art is that the level of PRO1800 protein expression would therefore also be increased in certain cancers. This conclusion is supported by two expert affidavits. (See Grimaldi declaration, paragraph 5; Polakis declaration, paragraph 6). The PTO has not offered any support for its arguments to the contrary. It therefore follows that if the protein is overexpressed in certain cancers, antibodies to PRO1800 polypeptides would be useful as a cancer diagnostic tool. Thus, Applicants submit that the PTO

has failed to establish a *prima facie* case of lack of substantial utility, and even if it did, given the totality of the evidence provided, Applicants submit that they have established a substantial utility for the claimed antibodies as a diagnostic agent.

Specific Utility

The PTO argues that even if substantial utility were found, there is no specific utility given for the antibody to the PRO1800 protein, since the protein has not been associated with any disease, condition, enzymatic activity or any other specific feature. The PTO quote the utility guideline training materials which note that "Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed." The PTO argues that here, there is no disclosure of any condition that can be diagnosed, and therefore no specific utility. The PTO also argues that the current situation closely tracks Example 4 of the utility guidelines, where a protein of unknown function was characterized as lacking utility. Applicants respectfully disagree.

Specific Utility is defined as utility which is "specific to the subject matter claimed," in contrast to "a general utility that would be applicable to the broad class of the invention." M.P.E.P. § 2107.01 I. Applicants submit that the evidence of overexpression of the gene which encodes PRO1800 in certain types of cancer cells, along with the declarations discussed above, provide a specific utility for the claimed antibodies to the protein. As stated above, the general, accepted understanding in the art is that because the gene is overexpressed, the level of PRO1800 protein expression is also increased. This makes the PRO1800 protein, and antibodies to it, useful in diagnosing and further characterizing cancer. The substantial utilities described above are specific to the disclosed antibodies to the PRO1800 protein because there is evidence that PRO1800 is overexpressed in certain cancer cells compared to normal cells. This is not a general utility that would apply to the broad class of antibodies.

The overexpression of nucleic acid encoding PRO1800 in certain cancer cells distinguishes this case from Examples 4 of the Utility Guidelines cited by the PTO. In that example, there is no description of the protein beyond its sequence. Here, the disclosed proteins are encoded by a nucleic acid that is overexpressed in certain cancer cells. This makes the utility of using antibodies to the protein to diagnose and type cancer cells specific, since as a general class, antibodies are not directed to proteins that are overexpressed in cancer cells.

Conclusion

The PTO has asserted three arguments for why there is a lack of a substantial utility: (1) that the data reporting overexpression of the gene encoding PRO1800 in certain cancers is not significant, reproducible, or real; (2) that even if the overexpression data is significant, there is no necessary correlation between gene expression and mRNA or protein levels; and, (3) that many genes are irrelevant in microarrays, and therefore the gene encoding PRO1800 is irrelevant. Applicants have addressed each of these arguments in turn.

First, the Applicants provide a declaration stating that the data in Table 7 (Table 8 as amended) reporting overexpression of the gene is real and significant. The PTO has offered no reason to reject this portion of the Goddard Declaration. Next, the Applicants have shown that the references cited by the PTO to support its conclusion that there is no necessary correlation between the level of gene expression and mRNA or protein expression do not support the PTO's position, and in fact support the Applicant's position. Applicants have presented the declarations of two experts in the field along with supporting references which establish that the general, accepted view of those of skill in the art is that overexpression of the gene leads to overexpression of the protein. Finally, Applicants have shown that while it is true that not all genes are relevant for all microarrays, none of the references cited by the PTO offer any support for the conclusion that the gene encoding PRO1800 would not be useful as a cancer diagnostic tool, particularly for lung and colon cancer. In fact, the PTO's references support the Applicants' assertion that the overexpression of the gene encoding PRO1800 in certain cancers makes it useful as a diagnostic tool. Additionally, Applicants have provided the declarations of two experts in the field that state that the gene encoding PRO1800 is useful as a cancer diagnostic tool.

The PTO also asserts that even if a substantial utility is found for the PRO1800 antibodies, there is no specific utility because the PRO1800 protein has not been associated with any disease, condition, enzymatic activity or any other specific feature. Applicants have pointed out that substantial utilities described above are specific to the disclosed antibodies to the PRO1800 protein because there is evidence that PRO1800 is overexpressed in certain cancer cells compared to normal cells. This is not a general utility that would apply to the broad class of antibodies.

Thus, given the totality of the evidence provided, Applicants submit that they have established a specific and substantial credible utility for the claimed antibodies as a diagnostic agent. According to the PTO Utility Examination Guidelines (2001), irrefutable proof of a claimed utility is not required. Rather, a specific and substantial credible utility requires only a "reasonable" confirmation of a real world context of use. Applicants submit that they have established that it is more likely than not that one of skill in the art would reasonably accept the utility for the antibodies to the PRO1800 polypeptide set forth in the specification. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Rejection under 35 U.S.C. §112 – Enablement

The PTO rejected Claims 22-27 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. The PTO correctly cites *In re Wands* and the factors set forth therein to determine the scope of enablement. However, Applicants respectfully submit that the PTO's conclusions are not in line with the teachings of *Wands*.

For example, given the recent advances in the science of molecular biology, the unpredictability of this art has lessened significantly. As a result, the number of experiments necessary to determine a particular result is now low, and these experiments have become routine in the art. The PTO concedes that the level of skill in this art is very high, and thus ordinary artisans are expected to be adept in various methodologies in this art and practice them routinely.

In addition, the PTO relies heavily on the arguments discussed above in the section on substantial utility to suggest that the art is unpredictable. The PTO again asserts that many genes are irrelevant in microarrays, relying on the same three references discussed above. Applicants have addressed this argument at length above, and assert that the same arguments are applicable here. Next, the PTO asserts that there is no necessary correlation between gene overexpression and mRNA or protein overexpression, again relying on the same references as in the section on substantial utility. Applicants have also addressed this argument at length above, and assert that the same arguments are applicable here.

Applicants believe that the arguments and declarations discussed above make clear that evidence of overexpression of the gene encoding PRO1800 in cancer is significant, and that the

general understanding of those of skill in the art would be that the PRO1800 proteins and antibodies have a specific and substantial use in the diagnosis and characterization of cancer cells. This would include, for example, the use of the antibodies to the PRO1800 protein for the diagnosis of cancer or further characterization of cancer cells. Use of the antibodies as a diagnostic tool is disclosed in the application, for example at page 98, lines 6-18 of the specification, and the techniques for creating and use of antibodies to detect the presence of specific proteins in tissue are well-known and routine in the art. Thus, at least one use of the antibodies to the PRO1800 protein is adequately enabled, which is all that is required – "if any use is enabled when multiple uses are disclosed, the application is enabling for the claimed invention" (M.P.E.P. § 2164.01(c)).

Further, the Federal Circuit in *Noelle v. Lederman* (355 F.3d 1343 (Fed. Cir. 2004)), confirmed that "as long as an applicant has disclosed a 'fully characterized antigen,' either by its structure, formula, chemical name, or physical properties, or by depositing the protein in a public depository, the applicant can then claim an antibody by its binding affinity to that described antigen" (emphasis in original). Since the PRO1800 antigen has been fully characterized, Applicants are entitled to claims directed to antibodies capable of binding to PRO1800.

In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw the enablement rejection under 35 U.S.C. § 112, first paragraph.

CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: August 30, 2004

By: _____

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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

COPY

Applicant	:	Botstein, et al.
Appl. No.	:	10/032,996
Filed	:	December 27, 2001
For	:	SECRETED AND TRANSMEMBRANE POLYPEPTIDES AND NUCLEIC ACIDS ENCODING THE SAME
Examiner	:	Fredman, J.
Group Art Unit	:	1634

DECLARATION OF PAUL POLAKIS, PH.D. UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Attached is the Declaration of Paul Polakis, Ph.D.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: June 16, 2004

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DECLARATION OF PAUL POLAKIS, Ph.D.

I, Paul Polakis, Ph.D., declare and say as follows:

1. I was awarded a Ph.D. by the Department of Biochemistry of the Michigan State University in 1984. My scientific Curriculum Vitae is attached to and forms part of this Declaration (Exhibit A).

2. I am currently employed by Genentech, Inc. where my job title is Staff Scientist. Since joining Genentech in 1999, one of my primary responsibilities has been leading Genentech's Tumor Antigen Project, which is a large research project with a primary focus on identifying tumor cell markers that find use as targets for both the diagnosis and treatment of cancer in humans.

3. As part of the Tumor Antigen Project, my laboratory has been analyzing differential expression of various genes in tumor cells relative to normal cells. The purpose of this research is to identify proteins that are abundantly expressed on certain tumor cells and that are either (i) not expressed, or (ii) expressed at lower levels, on corresponding normal cells. We call such differentially expressed proteins "tumor antigen proteins". When such a tumor antigen protein is identified, one can produce an antibody that recognizes and binds to that protein. Such an antibody finds use in the diagnosis of human cancer and may ultimately serve as an effective therapeutic in the treatment of human cancer.

4. In the course of the research conducted by Genentech's Tumor Antigen Project, we have employed a variety of scientific techniques for detecting and studying differential gene expression in human tumor cells relative to normal cells, at genomic DNA, mRNA and protein levels. An important example of one such technique is the well known and widely used technique of microarray analysis which has proven to be extremely useful for the identification of mRNA molecules that are differentially expressed in one tissue or cell type relative to another. In the course of our research using microarray analysis, we have identified approximately 200 gene transcripts that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. To date, we have generated antibodies that bind to about 30 of the tumor antigen proteins expressed from these differentially expressed gene transcripts and have used these antibodies to quantitatively determine the level of production of these tumor antigen proteins in both human cancer cells and corresponding normal cells. We have then compared the levels of mRNA and protein in both the tumor and normal cells analyzed.

5. From the mRNA and protein expression analyses described in paragraph 4 above, we have observed that there is a strong correlation between changes in the level of mRNA present in any particular cell type and the level of protein

expressed from that mRNA in that cell type. In approximately 80% of our observations we have found that increases in the level of a particular mRNA correlates with changes in the level of protein expressed from that mRNA when human tumor cells are compared with their corresponding normal cells.

6. Based upon my own experience accumulated in more than 20 years of research, including the data discussed in paragraphs 4 and 5 above and my knowledge of the relevant scientific literature, it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell. In fact, it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein. While there have been published reports of genes for which such a correlation does not exist, it is my opinion that such reports are exceptions to the commonly understood general rule that increased mRNA levels are predictive of corresponding increased levels of the encoded protein.

7. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information or belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful statements may jeopardize the validity of the application or any patent issued thereon.

Dated: 5/07/04

By: Paul Polakis

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CURRICULUM VITAE

PAUL G. POLAKIS
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EDUCATION:

Ph.D., Biochemistry, Department of Biochemistry,
Michigan State University (1984)

B.S., Biology. College of Natural Science, Michigan State University (1977)

PROFESSIONAL EXPERIENCE:

2002-present	Staff Scientist, Genentech, Inc S. San Francisco, CA
1999- 2002	Senior Scientist, Genentech, Inc., S. San Francisco, CA
1997 -1999	Research Director Onyx Pharmaceuticals, Richmond, CA
1992- 1996	Senior Scientist, Project Leader, Onyx Pharmaceuticals, Richmond, CA
1991-1992	Senior Scientist, Chiron Corporation, Emeryville, CA.
1989-1991	Scientist, Cetus Corporation, Emeryville CA.
1987-1989	Postdoctoral Research Associate, Genentech, Inc., South SanFrancisco, CA.
1985-1987	Postdoctoral Research Associate, Department of Medicine, Duke University Medical Center, Durham, NC

1984-1985	Assistant Professor, Department of Chemistry, Oberlin College, Oberlin, Ohio
1980-1984	Graduate Research Assistant, Department of Biochemistry, Michigan State University East Lansing, Michigan

PUBLICATIONS:

1. **Polakis, P G.** and Wilson, J. E. 1982 Purification of a Highly Bindable Rat Brain Hexokinase by High Performance Liquid Chromatography. **Biochem. Biophys. Res. Commun.** 107, 937-943.

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5. **Polakis, P.G.**, Uhing, R.J. and Snyderman, R. 1988 The Formylpeptide Chemoattractant Receptor Copurifies with a GTP-binding Protein Containing a Distinct 40 kDa Pertussis Toxin Substrate. **J. Biol. Chem.** 263, 4969-4979.

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